TaPIR-Project

Gepubliceerd: 04-04-2017 Laatst bijgewerkt: 15-05-2024

Observational study. We aim to investigate (thermal) stability of the enzyme pyruvate kinase in haemoglobinopathies. Secondary, we aim to investigate the possibility of stimulating the PK activity and stability ex vivo by use of allosteric...

Ethische beoordeling	Niet van toepassing
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON24118

Bron
Nationaal Trial Register

Verkorte titel
TaPIR-Project

Aandoening

sickle cell anemia, sikkelcelziekte, sikkelcelanemie, sikkel cel, thalassemia, thalassemie, unstable Hb, instabiel hb, haemoglobinopathies, haemoglobinopathie

Ondersteuning

Primaire sponsor: Charles Kung, associate director Agios Pharmaceuticals
Overige ondersteuning: Agios pharmaceuticals

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Main objective:
- To investigate pyruvate kinase thermal stability in haemoglobinopathies.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:

Haemoglobinopathies encompass all genetic diseases of haemoglobin. Patients with haemoglobinopathies suffer from anaemia because of premature red blood cell destruction. The pathophysiology behind this is multifactorial and complex. However, increased oxidative stress is a common pathophysiologic feature that is shared by all haemoglobinopathies.

Pilot studies in our laboratory have shown that pyruvate kinase shows decreased stability in haemoglobinopathies. Since pyruvate kinase is essential for red blood cell energy supply and anti-oxidative defence we postulate that this instability could compromise red cell metabolism, and thereby, cellular survival. Also, by retrograde accumulation, loss of pyruvate kinase activity could lead to an increase in 2,3-DPG, which in turn is an important regulator of oxygen affinity of haemoglobin. Lowering 2,3-DPG levels is currently used as a therapeutic target in several clinical trials in sickle cell disease, a common form of haemoglobinopathy.

Currently, in our laboratory and clinic, pyruvate kinase-activators are tested that have been designed to treat the rare hereditary disease pyruvate kinase deficiency. Recently, the use of these allosteric activators has been extended to the field of thalassaemia, another common form of haemoglobinopathy. A study in a mouse model of thalassaemia showed successful stimulation of pyruvate kinase function resulting in increased haemoglobin levels in vivo. We therefore aim to further explore the role of decreased stability of PK in several forms of haemoglobinopathies in humans, and study the effect of restoring this instability by the use of allosteric activators ex vivo.

Objective:

Main objective:

- To investigate pyruvate kinase thermal stability in haemoglobinopathies.

Secondary objectives:

- To investigate the possibility of stimulation of PK activity and thermal stability by use of allosteric activators

- To investigate oxidative stress as a cause of decreased pyruvate kinase thermal stability in haemoglobinopathies

- To investigate the role of PK thermal stability related to clinical symptoms and disease severity

Study design: Case control study

Study population:

45 adult haemoglobinopathy patients, 15 hereditary anemia patients and 10 healthy controls.

Intervention (if applicable): not applicable

Main study parameters/endpoints:

Pyruvate kinase thermal stability, pyruvate kinase activity, 2,3-DPG/ATP, Emden Meyerhof pathway enzymes, reactive oxygen species, methaemoglobin

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients and healthy controls are asked for a single blood donation of 57 ml via venepuncture. Physical discomfort may include bruising. Also patients are asked permission for medical chart review.

Doel van het onderzoek

Observational study. We aim to investigate (thermal) stability of the enzyme pyruvate kinase in haemoglobinopathies. Secondary, we aim to investigate the possibility of stimulating the PK activity and stability ex vivo by use of allosteric activators. We aim to ibvestigate oxidative stress as a cause of decreased stability and we aim to investigate the role of PK thermal stability related to clinical symptoms and disease severity.

Onderzoeksopzet

enrollment, end of study

Onderzoeksproduct en/of interventie

No intervention. This is an observational study

Contactpersonen

Publiek

UMC Utrecht

HAS van Straaten
Utrecht
The Netherlands

Wetenschappelijk

UMC Utrecht

HAS van Straaten
Utrecht
The Netherlands

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Adult patients (18 years or older) with a diagnosis as listed above

- Participant is willing and able to give informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Exclusion criteria:

- Inability to give informed consent.

- Need for regular red blood cell transfusions (more than 8 transfusions a year)

- Recent transfusion, defined as within 2 months prior to enrolment).

The last two criteria do not lead to exclusion for patients with Unstable Hb, because of the extreme rarity of the diagnosis.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-09-2017
Aantal proefpersonen:	55
Type:	Verwachte startdatum

Ethische beoordeling

Niet van toepassing

Soort:	Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 55777
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6288
NTR-old	NTR6462
CCMO	NL59957.041.17
OMON	NL-OMON55777

Resultaten

Samenvatting resultaten
to be expected